Remarks

Claims 1-17, 25-34, and 36-47 are pending in this application. The amendments made herein to the claims do not incorporate new matter into the application as originally filed. Support for the amendments can be found in the drawings and throughout the instant specification. Applicants have amended Claims 1, 15, 32 and 38 to clarify that the penetration depth of the needle with respect to the limiter is set during manufacture of the assembly.

As an initial matter, Compounds (referred to as "injectates") can be injected into different tissue spaces. For certain injectates, the delivery route will affect the body's response to the injectate. The most commonly used routes of administration are intramuscular (IM) and subcutaneous (SC) injections (*i.e.,* injections *below* the skin). These modes of delivery can be achieved relatively easily with traditional devices in light of the nature of the tissue into which delivery occurs. Intradermal delivery (that is, delivery into the intradermal space of the skin, referred to as "ID delivery" herein) is more difficult because of the nature of skin. In certain circumstances, however, ID delivery can provide an attractive response by the body.

By way of background, human skin is composed of two major tissue layers, an outer epidermis, and an underlying dermis. The epidermis of human skin is made up of five layers (the outermost impermeable barrier is called the stratum corneum) and has a total thickness of about 75 μm to 150 μm. The dermis lies beneath the epidermis, beginning at a depth of about 60 μm -- 120μm below the skin surface, and is approximately 1-2mm thick. The dermis contains two layers - the uppermost portion contains a bed of capillary and lymphatic vessels. The lower layer is relatively avascular, composed of dense connective tissue. Beneath the epidermis and dermis is the subcutaneous tissue, composed of connective tissue and fatty tissue. Muscle tissues lies beneath the subcutaneous tissue.

The present invention relates to devices for delivering injectates to the **intradermal compartment of human skin**. The space in the intradermal compartment that is targeted in accordance with the invention is close to the capillary bed, allowing for absorption and distribution of the substance in the body, but is above the peripheral nerve net, thereby eliminating or reducing injection pain. **The claimed invention is solely directed to *intradermal* delivery and placement of a needle such that the penetration depth of the needle is into the**

skin of the subject and is limited to the dermis layer of the skin of the subject. Such features are desirably achieved by the claimed invention by employing, *inter alia*, a limiter that is at a fixed, predetermined position with respect to the rest of the device. Such relationship provides the precise dimensions required for effective ID delivery with minimal leakage without the uncertainty inherent (and, likely, additional manufacturing expense) in any adjustable devices. As discussed below, the prior art does not teach or suggest a commercially reasonable device that can achieve effective intradermal delivery on a consistent basis.

Historically, intradermal injection has been attempted employing the "Mantoux" technique. This requires inserting a standard needle syringe at about a 15 degree angle to the surface of the skin, guiding the needle so that the outlet of the needle is situated in the intradermal space (and only in the intradermal space), and injecting at a rate controlled so that the injectate was not forced into other tissue spaces. Even when employed effectively, this technique raised concerns about leakage to the surface of the skin or into other tissues of the body. It is also noted that, in certain circumstances using this Mantoux technique, if the needle was originally inserted too deeply and withdrawn back into the intradermal space, the injectate may be delivered to the subcutaneous tissue rather than the intradermal space. Consequently, a new injection location would need to be selected.

The Applicant has found that it is possible to target injectate delivery into the intradermal space (intradermal compartment) reproducibly with the claimed device, such that leakage of the injectate back out through the skin or into other tissue spaces (and the associated variability in injectate dosage) is substantially eliminated. Using the device of the invention, even operators who have minimal training can perform effective intradermal delivery. (Data is available upon request.) Such advantages could not have been predicted from any of the cited documents and, accordingly, the present invention involves an inventive step. Furthermore, none of the prior art suggests the structural features or requirements of a device or method to accurately and reproducibly facilitate injectate delivery into the intradermal compartment, or the technical requirements that may be required in order to achieve intradermal delivery.

The Examiner erroneously contends the nature of the problem to be solved is that the injection is to be performed substantially with a non-movable limiter at the time of injection and

allows the operator to pre-select the depth of insertion of the needle; and as a result, the instant invention is non-obvious over these user-settable devices. This assumption is incorrect. The nature of the problem to be solved is achieving effective and accurate delivery to the intradermal space of a patient's tissue without requiring sophisticated injection techniques or depth setting by caregivers.

Request for Status and Clarification of Claims 38-47.

Claims 38-47 were presented and paid for in an Office Action Response dated July 7, 2005 in which Applicant had added New Claims 38-47 to the application. In the previous office action responses dated May 1, 2006 and December 7, 2006, Applicant had asserted that Claims 38-47 should be allowed. In this office action it appears that Claims 38-47 were unexamined. Applicant's representative left a voicemail message for the Examiner to clarify the status of these Claims on September 18, 2007. Applicant respectfully requests Examination and Clarification of the Status of Claims 38-47. According to MPEP 707.07(i), each pending claim should be mentioned by number, and its treatment or status given. Each action should include a summary of the status of all claims presented for examination.

Claim Rejections under 35 USC 103

In the Office Action, the Examiner has rejected claims 1-17, 25-34 and 37 under 35 U.S.C. §102(b) as unpatentable over U.S. Patent 3,073,306 to Linder (hereinafter "Linder") or U.S. Patent 5,873,856 to Hjertman et al. (hereinafter "Hjertman") or U.S. Patent 4,373,526 to Kling (hereinafter "Kling") in view of Japanese Publication 2000-37456 (hereinafter "TERUMO") or WO 99/34850 (hereinafter "FIDERM").

Thus, applicant respectfully submits that the shortcomings of Linder, Hjertman, and Kling individually are not overcome by the teachings or suggestions of combinations or modifications of the three cited references. Furthermore, the Examiner turns to TERUMO or FIDERM for proposed modifications and/or combinations of Linder, Hjertman, TERUMO, FIDERM and Kling to render the Applicant's invention obvious. Applicant contends Linder, Hjertman, and Kling teach an injection device having a movable limiter that controls the depth of injection of the needle to the screw-adjustable (Linder) or subcutaneous (Hjertman and Kling) or intramuscular (Kling) areas of the skin. Furthermore, Applicant contends TERUMO and

FIDERM teach injection devices having a different target area (subcutaneous) and do not provide for repeatable delivery to the intradermal portion of the skin.. Applicant respectfully submits that such teachings do not render the present claims of the present application obvious. Applicant's invention is directed to an intradermal delivery device for making intradermal injections that comprises, *inter alia*, a non-movable limiter which is set at the time of manufacture and that limits penetration of the needle to the dermis layer of the skin. Applicant respectfully submits that none of the cited art references relied upon by the Examiner in the Office Action, nor any other prior art references of record in the present application, teach or suggest such a device.

Applicant has discussed Linder, Hjertman, and Kling in previous office action responses and will discuss TERUM and FIDERM below. The limiter disclosed in FIDERM is generally concave and has a curved foraminous structure. Since FIDERM does not disclose or suggest a needle extending away from the skin engaging surface a pre-selected distance which is set during manufacture of the needle and limiter which results in intradermal delivery. FIDERM does not render the applicant's invention obvious. Furthermore, the needle of FIDERM allows for deformation of the skin (into the concave portion). The deformation does not allow for the precise needle depth placement for delivery into the intradermal space that the limiter structure of the applicant's invention provides. There is no teaching or suggestion in FIDERM much less dimensions requirements outlining the importance of the limiter/needle relationship in conjunction with a pre-selected injection depth.

With Respect to TERUMO, the device has an extension tube to limit the exposed length of needle to 0.05 – 3.0 mm **for subcutaneous delivery.** Furthermore, Terumo states in paragraph [0017] **"The height of the bulging epidermis is the intended depth of puncture. The depth of puncture varies on each occasion but it usually ranges from 0.05 to 3mm."** Thus the depth of injection of TERMO is variable, depending on the bulge. A variable injection depth does not result in proper intradermal delivery.

Applicant further respectfully submits that the Examiner has not made the required *prima facie* case of obviousness for claims 1-17, 25-34 and 37. See, e.g., MPEP §2142, 2143 et seq. Specifically, Applicant respectfully submits as discussed previously, that the Examiner has failed to show that the references teach or suggest all the claim limitations on a Claim by claim basis.

According to MPEP The Examiner states that "*a person of ordinary skill in the art, modifying the apparatuses disclosed by Linder, Hjertman et al. or Kling with a limiter having only one pre-selected depth for needle insertion , would have been considered obvious in view of the proven conventionality of this limiter design.*" However, as noted above, the disclosure of Linder, Hjertman, and Kling are specifically directed to movable limiters. Applicant submits that an obvious design choice for needle penetration depths according to the reference cited must provide for a subcutaneous or intramuscular injection utilizing a movable limiter. As noted above, injections in the range recited by applicants claims (e.g., equal to approximately 0.5 mm to approximately 3.0 mm) provide only for intradermal injections. **All five references are silent with regard to the desirability or requirements of intradermal injections and to the added limitation of dimensions set at manufacture.** Applicant respectfully submits that, based on the teachings of Linder, Hjertman, TERUMO, FIDERM and/or Kling as considered alone or in combination with each other (or with any other cited reference in the present application), a person of ordinary skill in the art would not conclude that a predetermined and set at manufacture needle penetration range including 0.5 mm to approximately 3.0 mm would be an obvious design choice for any of the devices disclosed by Linder, Hjertman, TERUMO, FIDERM and Kling, as such a range would not provide for subcutaneous/intramuscular injections with a movable limiter, as is clearly the intent of the cited references. Adjustable and slidable relationship between the limiter of these references and the devices of these references differentiate them from the Applicant's claimed invention. In these references, the device does not allow for precise setting of a preselected at manufacture injection depth. In contrast, Claims 1, 15, 32 and 38 as now amended, require a fixed relationship between the limiter and the needle. For the reasons cited previously with respect to adjustable limiters, the limiters of these disclosures do not teach or suggest the Applicant's invention as presently claimed.

Conclusion

In view of the Amendments submitted, Disclaimer filed previously and the Remarks above, Applicant respectfully submits that Claims 1-17, 25-34, and 36-47 are in condition for allowance, and respectfully requests that the Examiner earnestly reconsider his rejections of the present application. Applicant hereby authorizes the Commissioner to charge the fees necessary in connection with this Response, Extension of Time, and any other fees necessary in connection with this application, to Deposit Account Number 02-1666.

In light of the above amendments and remarks, Applicant respectfully requests that the Examiner enter the amendments and consider the remarks made herein. Consideration and prompt allowance of the claims are respectfully submitted.

Any questions concerning this application or amendment may be directed to the undersigned agent of applicant.

Respectfully submitted,

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